IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

REQUEST FOR FILING APPLICATION
Under Rule 53(a), (b) & (f)
(No Filing Fee or Oath/Declaration)
(Do NOT use for Provisional or PCT Applications)
Use for Design or Utility Applications

PATENT APPLICATION

RULE 53(f) NO DECLARATION

Assistant Commissioner of Patents
and Trademarks
Washington, DC 20231

Atty. Dkt. PM 260218 / M# | 97/20PCT/De / Client Ref.

Date: June 15, 1999

Sir:

1. This is a Request for filing a new Patent Application(☐ Design ☒ Utility) entitled:

2. (Complete) Title: CYCLOPHOSPHAMIDE FILM-COATED TABLETS

without a filing fee or Oath/Declaration but for which is enclosed the following:

3. ☒ Abstract 1 page(s).

4. 6 Pages of Specification (only spec. and claims); 5. ☐ Specification in non-English language

6. 4 Numbered claim(s); and

7. ☐ _____ sheet(s) per set: ☐ 1 set informal; 8. ☐ formal of size: ☐ A4 ☐ 11" Drawings:

9. **DOMESTIC/INTERNATIONAL** priority is claimed under 35 USC 119(e)/120/365(c) based on the following provisional, nonprovisional and/or PCT international application(s):

Application No.	Filing Date	Application No.	Filing Date
(1)		(2)	
(3)		(4)	
(5)		(6)	

10. **FOREIGN** priority is claimed under 35 USC 119(a)-(d)/365(b) based on filing in Germany

Application No.	Filing Date	Application No.	Filing Date
(1) 198 26 517.4	June 15, 1998	(2)	
(3)		(4)	
(5)		(6)	

11. 1 (No.) Certified copy (copies): ☒ attached; ☐ previously filed (date) _____ in U.S. Application No. / _____ filed on _____

12. ☐ This is a reissue of Patent No. _____

13. ☐ See top first page re prior Provisional, National, International application(s) (X box only if info is there and do not complete corresponding item 14 or 15.)

14. ☐ **Amend the specification** by inserting before the first line -- This is a ☐ Continuation-in-Part ☐ Divisional ☐ Continuation ☐ Substitute Application (MPEP 201.09) of:

14(a) ☐ National Appln. No. / _____ filed .- - (M#)

14(b) ☐ International Appln. No. PCT/ _____ filed _____

.--

15. ☐ **Amend the specification** by inserting before the first line: --This application claims the benefit of U.S. Provisional Application No. 60/ _____ , filed _____ .--

16. Extension to date: ☐ concurrently filed ☐ not needed ☐ previously filed

17. ☐ Prior application is assigned to

by Assignment recorded _____ Reel _____ Frame _____

18. ☒ **Attached: Verified Translation - Statement.**

19. This application is made by the following named inventor(s) **(Double check instructions for accuracy.):**

(1) Inventor	Jürgen		**Engel**
	First	Middle Initial	Family Name
Residence	Alzenau	Germany	Germany
	City	State/Foreign Country	Country of Citizenship
Post Office Address	Erlenweg 3, D-63755 Alzenau, Germany		
(include Zip Code)			

(2) Inventor	Jürgen		**Rawert**
	First	Middle Initial	Family Name
Residence	Alzenau	Germany	Germany
	City	State/Foreign Country	Country of Citizenship
Post Office Address	Bezirksstrasse 27, D-63755 Alzenau, Germany		
(include Zip Code)			

(3) Inventor	Dieter		**Sauerbier**
	First	Middle Initial	Family Name
Residence	Werther	Germany	Germany
	City	State/Foreign Country	Country of Citizenship
Post Office Address	Rauhe Horst 18, D-33824 Werther, Germany		
(include Zip Code)			

(4) Inventor	Burkhard		**Wichert**
	First	Middle Initial	Family Name
Residence	Bielefeld	Germany	Germany
	City	State/Foreign Country	Country of Citizenship
Post Office Address	Roonstrasse 48, D-33615 Bielefeld, Germany		
(include Zip Code)			

(5) Inventor			
	First	Middle Initial	Family Name
Residence			
	City	State/Foreign Country	Country of Citizenship
Post Office Address			
(include Zip Code)			

20. NOTE: FOR ADDITIONAL INVENTORS, check box ☐
and attach sheet with same information regarding additional inventors.

Pillsbury Madison & Sutro LLP
Intellectual Property Group

1100 New York Avenue, N.W.
Ninth Floor, East Tower
Washington, D.C. 20005-3918
Tel: (202) 861-3000
Atty/Sec: KEJ/jns

By: Atty: Kevin E. Joyce Reg. No. **20508**

Sig: By [signature] 28458

Fax: (202) 822-0944
Tel: (202) 861-3050

NOTE: File in duplicate with 2 post card receipts (PAT-103) & attachments

IN THE UNITED STATES PATENT OFFICE

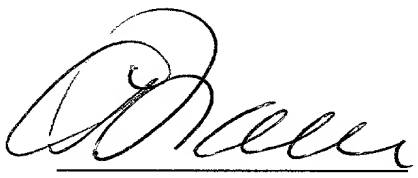
I, Stephen DRANE BSc PhD BDÜ,
translator to RWS Group plc, of Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England declare;

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland.

2. That I am well acquainted with the German and English languages.

3. That the attached is, to the best of my knowledge and belief, a true translation into the English language of the accompanying copy of the specification filed with the application for a patent in Germany on 15 June 1998 under the number 198 26 517.4 and the official certificate attached hereto.

4. That I believe that all statements made herein of my own knowledge are true and that all statements made on information and belief are true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardise the validity of the patent application in the United States of America or any patent issuing thereon.



For and on behalf of RWS Group plc
The 29th day of April 1999

FEDERAL REPUBLIC OF GERMANY

CERTIFICATE

ASTA Medica Aktiengesellschaft

of

Dresden/Germany

have filed a Patent Application under the title:

"Cyclophosphamide film-coated tablets"

on 15 June 1998 at the German Patent and Trademark Office.

The attached document is a correct and accurate reproduction of the original submission for this Patent Application.

The German Patent and Trademark Office has for the time being given the Application the symbol A 61 K 31/675 of the International Patent Classification.

Munich, 24 March 1999
German Patent and Trademark Office
The President
pp
Hoiß

File No: 198 26 517.4

APPLICATION UNDER UNITED STATES PATENT LAWS

Invention: CYCLOPHOSPHAMIDE FILM-COATED TABLETS

Inventor(s): Jürgen ENGEL
Jürgen RAWERT
Dieter SAUERBIER
Buckhard WICHERT

Pillsbury Madison & Sutro LLP
Intellectual Property Group
1100 New York Avenue, N.W.
Ninth Floor, East Tower
Washington, D.C. 20005-3918
Attorneys
Telephone: (202) 861-3000

This is a:

- ☐ Provisional Application
- ☒ Regular Utility Application
- ☐ Continuing Application
- ☐ PCT National Phase Application
- ☐ Design Application
- ☐ Reissue Application
- ☐ Plant Application
- ☐ Substitute Specification
  Sub. Spec. filed _____
  in App. No _____ / _____
- ☐ Marked Up Specification re
  Sub. Spec. filed _____
  in App. No. _____ / _____

SPECIFICATION

Cyclophosphamide film-coated tablets

The invention relates to cyclophosphamide film-coated tablets and to a process for their preparation. The invention can be used in the pharmaceutical industry.

Cyclophosphamide is an agent having a broad antitumor spectrum which has been introduced [sic] in chemotherapy for decades for the treatment of solid tumors such as mastocarcinoma, bronchial carcinoma and hemoblastoses.

Until now, on [sic] known pharmaceutical forms have been tablets, coated tablets and mainly lyophilizates with various auxiliaries such as mannitol or urea.

EP 0519099 describes tablets comprising cyclophosphamide and preswollen starch, prepared by a direct tableting process.
Since cyclophosphamide is dangerous to health and for this reason direct contact with this substance represents a potential risk, the tablets prepared according to EP 0519099 are used as cores for press-coated tablets and thus coated by means of a second tableting. This process is technically complicated. Special tableting machines are furthermore needed for the preparation of press-coated tablets.

The need thus exists for a simple and economical preparation of solid pharmaceutical form [sic] comprising cyclophosphamide for oral administration.
It is necessary to take into consideration here that the pharmaceutical forms have to be coated in order that direct contact with the cytotoxic active compound is avoided.
It is moreover known that cyclophosphamide is chemically labile, thus the stability of the pharmaceutical forms must also be taken into consideration.

Surprisingly, it has been possible to prepare film-coated tablets comprising cyclophosphamide without the use of preswollen starch.
Suitable auxiliaries were selected on the basis of the compatibility investigations mentioned in Example I [sic]. It was surprising in this context that the stability of cyclophosphamide is somewhat indifferent in the presence of preswollen starch.
It was moreover surprising that the finished film-coated tablets exhibit an adequate stability although the active compound, due to the preparation, is stressed during the film-coating process by moisture and heat.

Example 1

Investigations on the compatibility of cyclophosphamide with various tableting auxiliaries

53.5 mg of cyclophosphamide and 86.5 mg of (auxiliary 1-10) [sic] or 3.0 mg of (auxiliary 11-18) [sic] were in each case mixed and compressed. The pressed tablets were stored at 31°C for 6 months. The decomposition of the active compound was carried out [sic] by means of chloride determination.
The results are summarized in the following table.

Function of the auxiliary		Auxiliary	Decomposition of cyclo-phosphamide	Dis-coloration
FILLER	1	Lactose, anhydrous	2.52	++
	2	Calcium phosphate	3.85	-
	3	Calcium phosphate anhydrous	2.02	-
	4	Emcompress($CaHPO_4$)	1.50	
	5	D-mannitol	1.15	-
	6	Lactose monohydrate	0.70	-
FILLER/DRY BINDER/ DISINTEGRATION PROMOTER	7	Microcrystalline cellulose	1.50-1.73*	-
	8	Cellulose (Elcema)	0.85-1.32*	-+
	9	Preswollen starch	1.02	-+
	10	Cornstarch	0.75	-
DISINTEGRATION PROMOTER	11	Crosslinked poly-vinyl pyrrolidone	1.5	++
FLOW REGULATOR	12	Highly disperse silica	0.46-1.72*	-+
FLOW REGULATOR/ LUBRICANT	13	Magnesium stearate	1.51	-+
	14	Stearic acid	0.94	-+
	15	Glycerol palmitostearate	0.82	-
	16	Polyethylene glycol	0.68	-
	17	Talc	0.55	-
	18	Glycerol monobeherate [sic]	0.30	-

* Dependent on type

Example 2

Preparation of tablet cores (50 mg of cyclophosphamide)
Direct tableting

0.535 mg of cyclophosphamide, 0.390 mg of lactose monohydrate, 0.400 mg of microfine cellulose, 0.200 mg of cornstarch, 0.040 mg of talc and 0.020 mg of highly disperse silica are sieved and homogenized. 0.015 mg of magnesium stearate is then added and mixed. The mass prepared in this way is processed to give tablets:

Weight:	160 mg
Hardness:	> 30 N
Disintegration:	< 10 min.

Example 3

Preparation of film-coated tablets (50 mg of cyclophosphamide)

11.83 g of polyethylene glycol and 2.37 g of polysorbate 80 are dissolved in 75.21 g of water.
1.9 g of carboxymethylcellulose sodium are dissolved in 80.0 g of water. The solutions are brought together. 23.67 g of talc, 23.67 g of titanium dioxide and 0.24 g of simeticone [sic] are then added and the mixture is homogenized. 17.73 g of a 30% strength ethyl acrylate/methyl metharcrylate [sic] copolymer dispersion in water are then added. The tablet cores are then sprayed with the prepared suspension in a suitable apparatus:

Theoretical weight of a film-coated tablet: 166 mg

Example 4

Investigation of the stability of cyclophosphamide film-coated tablets

Decomposition of cyclophosphamide after 3 months		
	26°C/60% RH	31°C/40%
Batch 1	0.30	4.12
Batch 2	0.17	2.36

Stability of the film-coated tablets of up to 3 years is expected on storage at < 25°C.

Patent claims

1. A film-coated tablet with cyclophosphamide as active compound, comprising in the core cyclophosphamide, one or more fillers, one or more dry binders but no preswollen starch, flow regulators and lubricants.

2. The film-coated tablet as claimed in claim 1, comprising in the core as a filler lactose monohydrate, D-mannitol or $CaHPO_4$, nonpreswollen cornstarch or microfine cellulose as a dry binder, highly disperse silica as a flow regulator and magnesium stearate, stearic acid, glycerol palmitostearate, polyethylene glycol, talc or glycerol monobeherate [sic] as a lubricant.

3. The film-coated tablet as claimed in claim 2, where the cores can comprise the auxiliaries either individually or alternatively in any desired mixture.

4. The film-coated tablet as claimed in claims 1 to 3, comprising, per part of cyclophosphamide in the core, lactose monohydrate, microfine cellulose, nonpreswollen cornstarch, talc, highly disperse silica and magnesium stearate in the following ratio:
lactose monohydrate 0.2-1.5, preferably 0.5-1, particularly 0.73
microfine cellulose 0.2-1.5, preferably 0.5-1, particularly 0.74
nonpreswollen cornstarch 0.1-1.5, preferably 0.2-0.7, particularly 0.37
talc 0.01-1.5, preferably 0.05-0.08, particularly 0.07
highly disperse silica 0.01-0.1, preferably 0.01-0.5, particularly 0.04
magnesium stearate 0.01-0.1, preferably 0.01-0.05, particularly 0.03.

Abstract

1. [sic] The invention relates to film-coated tablets with cyclophosphamide as active compound, which in the core comprise cyclophosphamide, one or more fillers, one or more dry binders but no preswollen starch, flow regulators and lubricants.
According to a preferred embodiment of the invention, the core of the film-coated tablet comprises as a filler lactose monohydrate, D-mannitol or $CaHPO_4$, nonpreswollen cornstarch or microfine cellulose as a dry binder, highly disperse silica as a flow regulator and magnesium stearate, stearic acid, glycerol palmitostearate, polyethylene glycol, talc or glycerol monobeherate [sic] as a lubricant.